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This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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042004**INVENTOR(S)**

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Additional inventors are being named on the 1 separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)**AMINE CORE POLY(ESTER-ACRYLATE) AND POLY(ESTER-EPOXIDE) DENDRONS/DENDRIMERS AND****Direct all correspondence to: CORRESPONDENCE ADDRESS THEIR DERIVATIVES** Customer Number: 008131**OR**

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ENCLOSED APPLICATION PARTS (check all that apply)

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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[Page 1 of 2]

Respectfully submitted,

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Date April 20, 2004

REGISTRATION NO. MSH-294P
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[Page 2 of 2]

Number 2 of 2

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Applicant(s): Donald A. Tomalia, Douglas R. Swanson, Baohua Huang

Serial No.	Filing Date	Examiner	Docket No.	Group Art Unit
_____	<u>April 20, 2004</u>	_____	<u>MSH-294P</u>	_____

Invention: AMINE CORE POLY(ESTER-ACRYLATE) AND POLY(ESTER-EPOXIDE) DENDRONS/
DEMDRIMERS AND THEIR DERIVATIVES

I hereby certify that the followings correspondence:

new patent application consisting of 11 pages of specification, 4 pages of drawings containing 5 figures, certificate of mailing under rule 1.10, authorization to charge deposit account 13-2492 the sum of \$80.00 for the filing fee, return receipt postcard, 1 page information disclosure letter, 2 pages provisional application cover sheet, 3 pages application data sheet

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35 U.S.C. 122(b)(2)(B)(i)**

First Named Inventor	Donald A. Tomalia
Title	AMINE CORE POLY(ESTER-ACRYLATE) AND POLY(ESTER-EPOXIDE)DENDRONS/DENDRIMERS AND THEIR DERIVATIVES
Attorney Docket Number	MSH-294P

I hereby certify that the invention disclosed in the attached application has not and will not be the subject of an application filed in another country, or under a multilateral agreement, that requires publication at eighteen months after filing.

I hereby request that the attached application not be published under 35 U.S.C. 122(b).

April 20, 2004

Date

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989-631-4551

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Applicant may rescind this nonpublication request at any time. If applicant rescinds a request that an application not be published under 35 U.S.C. 122(b), the application will be scheduled for publication at eighteen months from the earliest claimed filing date for which a benefit is claimed.

If applicant subsequently files an application directed to the invention disclosed in the attached application in another country, or under a multilateral international agreement, that requires publication of applications eighteen months after filing, the applicant must notify the United States Patent and Trademark Office of such filing within forty-five (45) days after the date of the filing of such foreign or international application. Failure to do so will result in abandonment of this application (35 U.S.C. 122(b)(2)(B)(iii)).

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To whom it may concern:

Be it known that we, Donald A. Tomalia, residing in the City of Midland, County of Midland, State of Michigan, a citizen of the United States, Douglas R. Swanson, residing in the City of Mt. Pleasant, County of Isabella, State of Michigan, a citizen of the United States and Baohua Huang residing in the city of Mt. Pleasant, County of Isabella, State of Michigan, a citizen of People's Republic of China have invented new and novel classes of

**AMINE CORE POLY(ESTER-ACRYLATE) AND POLY(ESTER-EPOXIDE)
DENDRONS/DENDRIMERS AND THEIR DERIVATIVES**

10

the following of which is a specification therefor.

The present invention relates to poly(ester-acrylate) and poly(ester-epoxide) dendrons/dendrimers and their derivatives that are new classes of amine core dendrimers. These materials can be synthesized by so-called "pre-formed branch cell methods" 15 which appear to be uniquely influenced by "sterically induced stoichiometric (SIS) principles."

The invention contemplates the preparation of the dendron/dendrimers wherein precursor monoamino-, diamino- or poly(amino)- functional core materials are allowed to react with various branch cell reagents that will be described *infra*. The branch cell 20 reagents are dimensionally large, relative to the amine initiator core and when reacted, produce (generation = 1), dendrimers directly in one step.

BACK GROUND OF THE INVENTION

Dendrimers are described in the prior art as globular, nano-scale core-shell type macromolecules. They consist of two or more "tree-like dendrons," emanating from a single, central atom, atomic cluster, molecular or macromolecular structure called the core. They are comprised of radial layers of "branch cells" that are the main building blocks or repeat units of the dendritic structures. They are organized in mathematically precise dendritic (i.e. branch upon branch) type architectural arrangements, that give rise 25 to a series of regular, radially concentric layers of branch cells around the core, called generations (G). Dendrimers consist of three architectural components that include: (1) a core, (2) interior branch cells, and (3) surface or exterior branch cells.

Dendrons are the smallest constitutive components of a dendrimer that exhibit the same dendritic architectural arrangement as the dendrimer itself and are reminiscent of "a molecular tree." They may initiate (originate) from a single trunk or branch that emanates with "leaf-like" terminal functional groups that may be either reactive or inert.

5 A very good source of information and details on dendritic polymers may be found in DENDRIMERS AND OTHER DENDRITIC POLYMERS, Tomalia, D., and Frechet, J., (2001) John Wiley & Sons, Ltd, New York, N.Y.

The dendrimers and derivatives of the present invention are new classes of dendrimers that have not been described in the prior art.

10 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an illustration of the reaction scheme between a small core initiator , ethylenediamine (EDA), and a "branch cell reagent", namely, trimethylolpropane triacrylate.

15 Figure 2 is an illustration of the reaction scheme between another small core initiator and a "branch cell reagent", namely, trimethylolpropane triacrylate.

Figure 3 is an illustration of comparative gel electrophoresis results for acrylate-terminaed dendrimers from a 15% crosslinked homogeneous polyacrylamide gel (PAGE) using a known G= 2 to 6, poly(amidoamine) dendrimers (PAMAM's) as the standard.

20 Figure 4 is an illustration of the two products 1 and 2 that are obtained from EDA and HMDA, respectively, from Example 6.

Figure 5 is an illustration of coparative results for epoxide terminated dendrons (PAGE) using G = 2 to 6, poly(amidoamine) dendrimers (PAMAM's) as a standard.

THE INVENTION

Completely new classes of amine core dendrons and endrimers can be synthesized 25 by utilizing so-called "sterically induced stoichiometric principles" (SIS). This is accomplished by allowing various selected " branch cell reagents" that are dimensionally large, relative to the initiator core, to react with various cores to produce G = 1, dendrons/dendrimers directly in one step. It has been shown that subsequent reaction of these G = 1 acrylate or expoxide terminated dendrons/dendrimers with ethylenediamine 30 or other poly(alkylene) amines (e.g., TREN, tri(aminoethyl)(amine) produces the respective amine terminated dendrimers. Subsequent reaction of these amine terminated

dendrimers appropriate acrylate/epoxide tri/tetra-functional branch cell reagents will produce the higher generations (i.e., G = 2, 3, 4, etc.) acrylate or epoxide dendrons/dendrimers. Therefore, by selecting a core that is relatively small compared to the dimension of the branch cell reagent, one will expect a finite number of reactive sites 5 on the core to be inaccessible and non-reactive with the branch cell reagent. On the other hand, when the targeted initiator core is selected to be large, relative to the branch cell reagent, one should expect all reactive sites on the core to undergo reaction with the branch cell reagent to produce a generation = 1 dendrimer directly.

Therefore, in one embodiment, this invention deals with poly(ester-acrylate) and 10 poly(ester-epoxide) dendrimers that are formed from amine initiator cores and branch cell reagents, wherein the use of “sterically induced stoichiometric” (SIS) principles are utilized, that is, wherein cores that are relatively small compared to the dimension of the branch cell reagent are used.

In another embodiment, this invention deals with reactive intermediates 15 (precursors) poly(ester-acrylate) and poly(ester-epoxide) dendrimers that are stabilized (pacified) by conversion to various more stable derivatives by either ring opening or Michael's addition reaction of their terminal groups..

Yet another embodiment of this invention is a method of preparing poly(ester-acrylate) and poly(ester-epoxide) dendrimers in a one step method and another 20 embodiment of this invention is a method of preparing stabilized poly(ester-acrylates) and poly(ester-epoxides) derivatives.

It is anticipated that any tri-functional or higher (BCR) (i.e., N_b greater than or equal to 2 after reaction possessing appropriate terminal groups that will react with the core and subsequent dendrimer surfaces, could be used to extend this invention to many 25 other non-amine cores.

DETAILED DESCRIPTION OF THE INVENTION

There is provided a method for preparing a dendrimer, the process comprising contacting a branch cell reagent with a diamine that is reactive with the branch cell reagent and allowing the branch cell reagent and the diamine to react for a time sufficient

and a temperature sufficient in the presence of a solvent to form a dendrimer selected from the group consisting of a poly(ester-acrylate) dendrimer and a poly(ester-epoxide) dendrimer.

Initiator cores that are useful in this invention are any primary or secondary amine substituted materials that will undergo reaction with the selected “branch cell reagents”, for example, ammonia, hydrazines, alkylene diamines such as ethylenediamine, hexamethylenediamine, octamethylenediamine, and poly(alkylene)-poly(amine) such as poly(ethyleneimine), poly(propyleneimine) and pendant amine containing polymers of all four architectural types including; (e.g. linear, bridged (cross-linked), branched and dendritic) and the like.

Branch cell reagents that are useful in this invention are tri and tetra-functional reagents normally thought of as having reactive unsaturated groups, thiols, carboxylates or heterocyclic rings (e.g. aziridinyl, epoxy, 2-oxazolinyl, etc. groups attached thereto and which are collectively large in size compared to the initiator cores used herein. Such materials are for example, tri-/tetra acrylates/methacrylates, for example, trimethylolpropane triacrylate or tri-/tetra-epoxides. When the “branch cell reagent” is tri-functional (i.e., tri-acrylate), the resulting branch cell after reaction will have a multiplicity $N_b = 2$. When a tetra-functional reagent is used, the resulting branch cell multiplicity after reaction will be $N_b = 3$. For example, a tri/tetra functional epoxide or acrylate (BCR) could be allowed to react with a thio or polythiol functionalized core to produce a thioether dendron/dendrimer possessing acrylate or epoxide terminal groups.

In the preparation of the dendrimers, the initiator cores and the branch cell reagents are contacted with each other in the presence of alcohols (i.e. methanol, etc) and polar/non-polar solvents depending upon the hydrophobic/hydrophilic nature of the reagents.

The reaction times for the reactions vary from a few minutes, to several hours, for example from $\frac{1}{2}$ hour to 30 hours. Preferred for this invention is a reaction time of less than 18 hours, and more preferred is a reaction time of less than 12 hours.

The reaction temperatures for the reaction can vary from about 20°C to about 150°C and preferred for this reaction is a temperature of about 25°C to about 75°C and most preferred is a reaction temperature of about 25°C to about 40°C.

Polar solvents are useful in this invention and preferred solvents are alcohols, preferably aliphatic alcohols, namely, methanol and ethanol.

It is preferred that the reactions be carried out under an inert atmosphere, and preferred for this reaction is nitrogen.

5 After the reaction has proceeded for the desirable amount of time, the reaction mass is cooled and the reaction mass is poured into another portion of and appropriate solvent (e.g. ethyl acetate, etc.) or alcohol to help facilitate the separation of the desired product. Thereafter, it is best to allow the solvated material to stand at room temperature, at which time the reaction mass separates into two layers and the methanol layer is
10 decanted from the other layer. For purposes of this invention, this part of the separation process should be performed once or twice more to help wash the crude product.

Thereafter, the non-decanted phase is subjected to the removal of volatiles therefrom, such as by evacuation using vacuum. During this stage of the work up of the product, the obtained crude product should be protected from light, as light tends to
15 degrade the products. The resulting products are poly(ester-acrylate) or poly(ester-epoxy) dendrimers, which are usually isolated as colorless liquids/oils. With regard to the poly(ester-octa-acrylate) product, (tetra adduct), allowing the products from this reaction to stand in solution for prolonged periods of time, or any attempt to remove solvent at room temperature may lead to the formation of white, insoluble crosslinked materials.

20 Therefore, these dendritic materials should be further treated with surface pacifying reactants by using Michaels adduct reaction schemes. For example, materials such as amines and thiols can be reacted with these surface unsaturated or epoxy functionalized dendrimers using stoichiometric amounts of materials such as monoethanolamine, mercaptoethanol or morpholine to provide stabilized dendrimers
25 derivatives and thus, these more robust, less reactive materials can be worked up with standard procedures to obtain useable products.

The following examples should not be construed as limiting the invention disclosed and claimed herein.

EXAMPLES

Example 1.

Preparation of [Ethylenediamine]; G = 1, *dendri*{CH₂-CH₂-CO₂-CH₂C(CH₃CH₂)(CH₂OC=(O)CH=CH₂)₂}₃ (hexa-acrylate adduct)

5 The reaction scheme for this example is set forth in Figure 1. To a 100 ml. round bottomed flask equipped with a stir bar was added trimethylolpropane triacrylate (29.6 g, 0.10 mol); 15 ml of methanol cooled to about 4°C, and ethylenediamine (EDA)(1.2 g, 0.02 mol) in 5 ml of methanol over about a 5 minute period. This mixture was stirred at 30°C for 18 hours. This mixture was cooled to 20°C and poured into 150 g of stirred
10 methanol. The product phased out after allowing the mixture to stand without stirring for 1 hour at room temperature. The supernatant methanol layer was decanted and this process was repeated two more times. This resulting clear, viscous phase was evacuated at high vacuum (2 to 3 mm) for 3 hours while protecting the reaction mass from light with aluminum foil wrapped around the reaction vessel, to give 20 g of product. The
15 yield was 100% based on tri-adduct(hexa-acrylate) and 80% yield based on tetra-adduct(octa-acrylate). The isolated product weight suggests that most of the material was the hexa-acrylate (tri-adduct) product consisting of three trimethylolpropane triacrylate molecules added to one EDA. A MALDI-TOF mass spectrum of this product indicated a major peak at 950 am μ corresponding to a hexa-acrylate (tri-adduct) product with a
20 theoretical molecular weight of 949. A small peak at 1245 am μ was observed consistent with the octa-acrylate (tetra-adduct) product. ¹³C-NMR (500 MHz, CDCL₃) δ 172.10, 165.69, 131.26, 128.04, 64.05, 63.88, 49.48, 40.86, 40.77, 32.38, 23.14, 23.00, 7.45.

Example 2.

Preparation of hexa-mercaptoethanol surface by pacification of Example 1

25 **Product.**
To a 250 ml round-bottomed flask equipped with a stir bar was added the ethylenediamine core poly(ester-acrylate) of example 1, (19 g, 20 mmol, 120 mmol acrylate in 50 ml of DME) and mercaptoethanol (10.4 g, 132 mmol, 1.1 equivalents per acrylate group) in 20 ml of DME. This mixture was stirred for 2 days at room
30 temperature. This mixture was stripped of volatiles on a rotary evaporator. The resulting material was mixed with 150 ml of ethyl acetate and rapidly stirred with a stir bar. This

heterogeneous mixture was allowed to settle for about 1 hour. The clear ethyl acetate layer was decanted. This process was repeated two more times. A PAGE of this material on a 15% crosslinked homogeneous polyacrylamide gel with PAMAM dendrimer standards G = 2 to 6 indicated a sharp, tight band corresponding to a G = 1 PAMAM

5 dendrimer. See Figure 3.

Example 3 Preparation of [Hexamethylenediamine]; G = 1, *dendri{CH₂-CH₂-CO₂-CH₂C(CH₃CH₂)(CH₂OC=(O)CH=CH₂)₂}*₄; (octa-acrylate adduct)

The reaction scheme for this example is set forth in Figure 2. To a 100 ml round-bottomed flask equipped with a stir bar was added trimethylolpropane triacrylate (29.6 g, 0.10 mol) and 10 ml of methanol. To this mixture, cooled at 4°C, was added hexamethylenediamine (2.32 g, 0.02 mol) in 20 ml of methanol. This mixture was heated at 30°C for 18 hours under N₂. This mixture was cooled to about 15°C and poured into 150 ml of stirred methanol. The product phased out by allowing this mixture to stand without stirring for 1 hour while protecting the flask from light by wrapping the reaction vessel with aluminum foil. The methanol layer was decanted and this operation was repeated two more times to give a clear, colorless, viscous liquid. This immiscible phase was devolatilized by evacuation at high vacuum (2 to 3 mm) for 3 to 5 hours to give 24 g (92% yield) of crude product whose isolated weight is consistent with an octa-acrylate (tetra-adduct) structure. A MALDI-TOF mass spectrum of this product indicated a small peak at 1301 am μ consistent with the tetra-adduct and several lower molecular weight peaks presumably derived from the “in-situ mass spectrometer decomposition” of the tetra-adduct structure. Allowing this product to stand in solution for prolonged periods of time or any attempt to remove solvent at room temperature, led to the formation of a white, insoluble crosslinked product. Therefore, this product was immediately converted

10 to a more stable Michaels adduct by allowing it to react with stoichiometric amounts of appropriate amine or thiol reagent as described in example 4 below.

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20

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Example 4

Preparation of Octa-monoethanolamine adduct via Michael addition of amine to the product of Example 3.

To a 250 ml round-bottomed flask containing a stir bar was added ethanolamine (27 g, 442 mmol, 3 equivalents per acrylate) in 50 ml of DMS. To this mixture cooled to

4°C was added hexamethylenediamine core; poly(ester-acrylate) from above, G = 1, octa-acrylate (24 g, 18.4 mmol, 8 acrylates per dendrimer) in 50 ml DME dropwise over about 10 minutes. This mixture was stirred at 25°C for 2 days under N₂. This mixture was stripped of volatiles with a rotary evaporator. This crude material was poured into a
5 rapidly stirred ethyl acetate. After a few minutes of stirring, the mixture was allowed to stand for 1 hour to allow separation of the two layers and the ethyl acetate layer was decanted. The same volume of ethyl acetate was added, the mixture rapidly stirred and separated as before. This was repeated a second time for a total of three washes. The clear, colorless viscous oil was evacuated at high vacuum overnight at room temperature
10 to give 29.7 g (90%) of the desired product. An analysis by PAGE on a 15% crosslinked homogeneous polyacrylamide gel using PAMAM dendrimers as standards (G = 2 to 6) indicated material that was a sharp, tight band corresponding to a G = 1 PAMAM dendrimer. See Figure 3 below.

Example 5.

15 **Preparation of the Octa-morpholine adduct of the material from example 3.**

To a 250 ml round-bottomed flask containing a stir bar was added poly(ester-acrylate) from example 3, G = 1, hexamethylenediamine core (24 g, 18.4 mmol, 147 mmol acrylate) in 50 ml of ethyleneglycol dimethyl ether (DME). To this mixture, cooled to about 40°C, was added morpholine (14 g, 160 mmol, 1.1 equivalents per acrylate) in
20 50 ml of DME over about 5 to 10 minutes. This mixture was warmed to room temperature and stirred for 24 hours. This mixture was stripped of volatiles on a rotary evaporator and high vacuum at 30°C for 18 hours to give a 34 g (94% yield) of product. A MALDI-TOF mass spectrum of this material showed a peak corresponding to the theoretical molecular weight of 1998 amu together with several lower peaks derived from
25 fragmentation of the 1998 amu peak. A ¹³C NMR spectrum of this material shows the product is very clean and consistent, with the correct number of carbons for the desired product. ¹³C NMR (500 MHz, CDCL₁₃) 172.16, 171.86, 71.79, 55.85, 63.56, 59.04, 53.94, 53.40, 48.97, 40.89, 40.78, 32.15, 27.54, 27.21, 22.82, 7.42. The PAGE results are shown in Figure 3 and columns 4 and 4' are smeared due to solubility.

POLY(ACRYLAMIDE) GEL ELECTROPHORESIS (PAGE)

All of the PAGES were run on 15% cross-linked homogeneous gels. As shown in Figure 3, columns 2 and 2' exhibit very tight bands that are the most mobile entities compared to the calibration ladders, i.e. PAMAM G = 2 to 6, in columns 1 and 1'. This 5 indicates a smaller size, consistent for this adduct versus the large octa-monoethanolamine adduct in columns 3 and 3'. Note that the octa-morpholine adduct in columns 4 and 4' are comparable in mobility to the octa-monoethanolamine adduct. However, the marginal solubility of the morpholine adduct in water exhibit smeared columns rather than the tight bands observed for the mercaptoethanol and the 10 ethanolamine adducts, that are more soluble in water.

Identification of the columns in Figure 3:

Column 1 = EA surface DAB Core Ladder G = 2 to 6

Column 2 = Example 2 product mercaptoethanol adduct

Column 3 = Example 4 product ethanolamine adduct

15 Column 4 = Example 5 product morpholine adduct

Column 1' = EA surface DAB Core Ladder G = 2 to 6

Column 2' = Example 2 product mercaptoethanol adduct

Column 3' = Example 4 product ethanolamine adduct

Column 4' = Example 5 product morpholine adduct

20 Example 6.

Preparation of [Ethylenediamine]; G = 1, *dendri*{CH₂-CH₂-CO₂-CH₂C(CH₃CH₂)(CH₂OCCH(O)CH₂)₂}_{3/4} ; (hexa-epoxide adduct) and (octa-epoxide adduct)

General procedure:

25 Trimethylolpropane triglycidyl ether (6.04g, 0.02mol) was dissolved in 15 ml. methanol and cooled to 0°C using an ice-water bath. To this cooled, stirred solution was added a solution of diamine (4mmol) (i.e. ethylenediamine/hexamethylenediamine) in 5mL methanol in a dropwise manner. After the addition, the reaction was allowed to warm to 30 room temperature and stirred for three hours. TLC indicated the reaction was proceeding slowly at room temperature. The reaction mixture was then heated to and maintained at

40°C overnight. Standard work-up as described in Examples above gave the products and yields described below:

1. **Ethylenediamine core:** The product was obtained as a clear oil, weight = 5.0 g, 90% yield.

5 2. **1,2-diaminohexane core:** the product was obtained as a slightly yellow oil, weight = 4.86 g 88% yield. See PAGE results and comparison to PAMAM dendrimers, G = 2 to 6 in Figure 5.

Figure 4 illustrates the results of an electrophoresis analysis wherein there was used 15% Homogeneous Gel with 0.1% sodium dodecyl sulfate (SDS); bromophenol dye
10 with 0.1% SDS was used.

In Figure 4, the following columns are shown:

Lane 1 DAB Core EA Surface Ladder G2-6
Lane 2 structure 1, epoxy surfaced product, 5 µL
Lane 3 structure 2, epoxy surfaced product, 5 µL
15 Lane 4 structure 1, morpholine adduct, 5 µL
Lane 5 structure 1, epoxy surfaced product, 2.5 µL
Lane 6 structure 2, epoxy surfaced product, 2.5 µL
Lane 7 structure 2, Morpholine adduct, 2.5 µL

20 In order to run a PAGE, the entire sample had to be dissolved in H₂O. The solubility of samples, structure 1, structure 2, and DRS-DNT25-45, in H₂O are poor. At the amount of 0.1% SDS (sodium dodecyl sulfate) added, the solubilities are all improved, but there are still small amounts of the samples that are not completely soluble in H₂O. This PAGE was run with partially dissolved sample. The results are shown in
25 Figure 5.

ABSTRACT

Poly(ester-acrylate) and poly(ester/epoxide) dendrimers. These materials can be synthesized by utilizing the so-called “sterically induced stoichiometric” principles. The 5 preparation of the dendrimers is carried out by reacting precursor amino/polyamino-functional core materials with various branch cell reagents. The branch cell reagents are dimensionally large, relative to the amino/polyamino- initiator core and when reacted, produce generation = 1 dendrimers directly in one step. There is also a method by which the dendrimers can be stabilized and that method is the reaction of the dendrimers with 10 surface reactive molecules to pacify the reactive groups on the dendrimers.

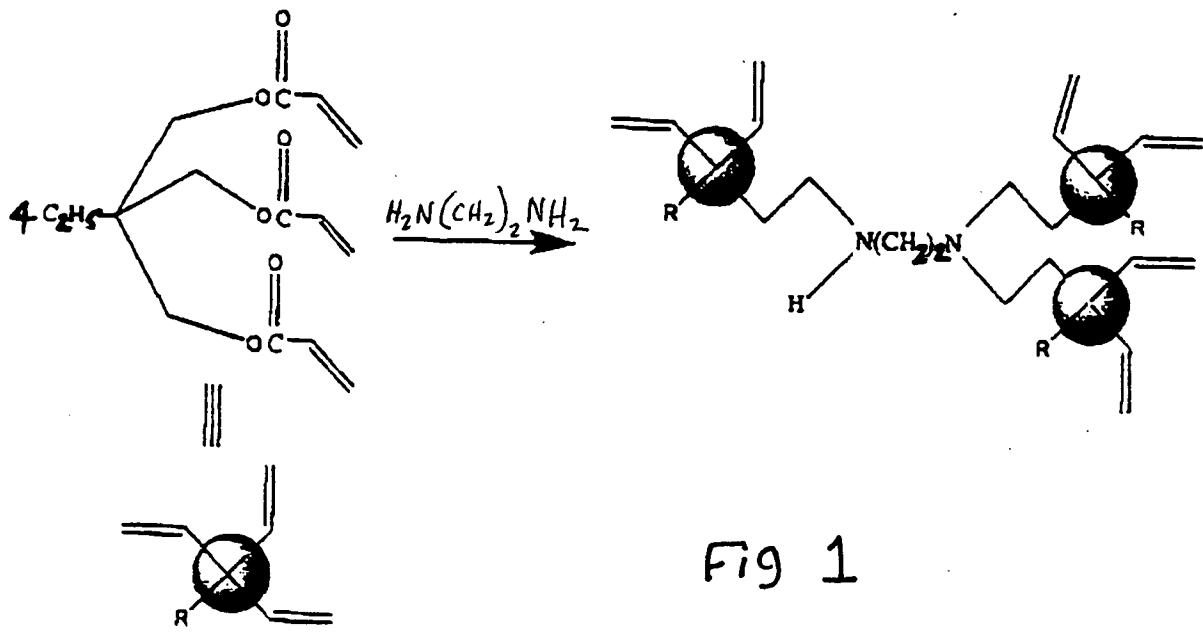


Fig 1

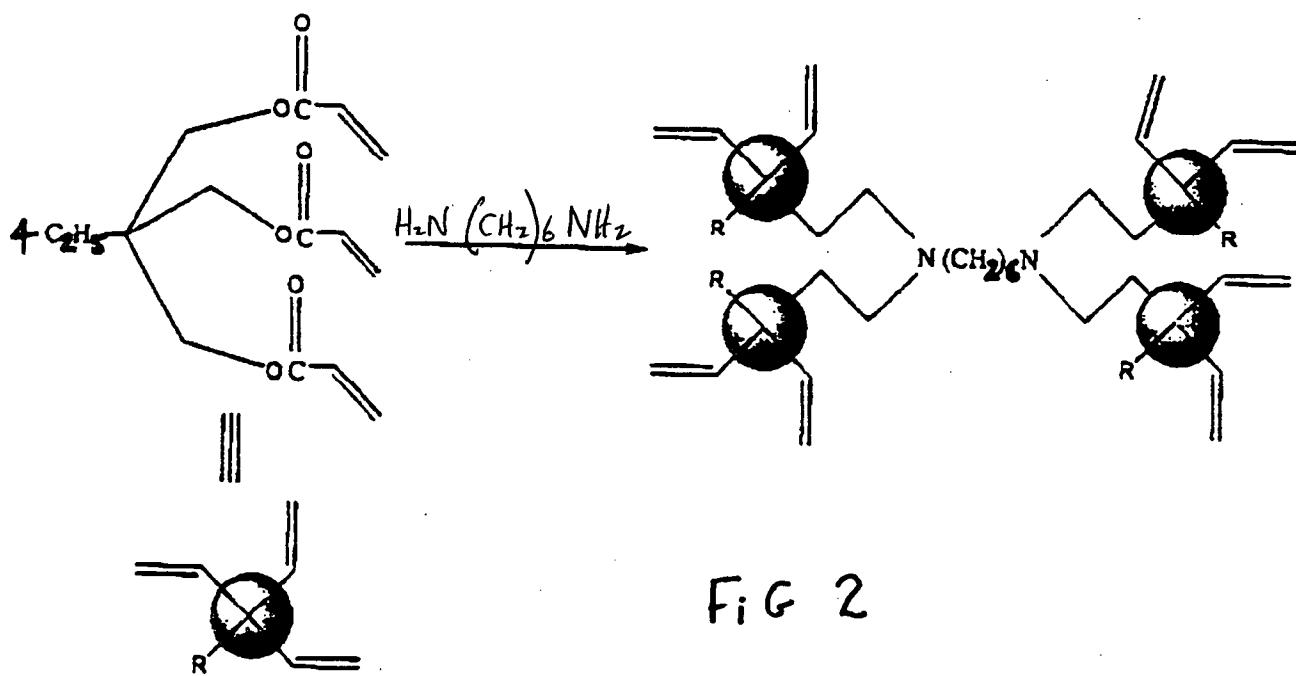


Fig 2

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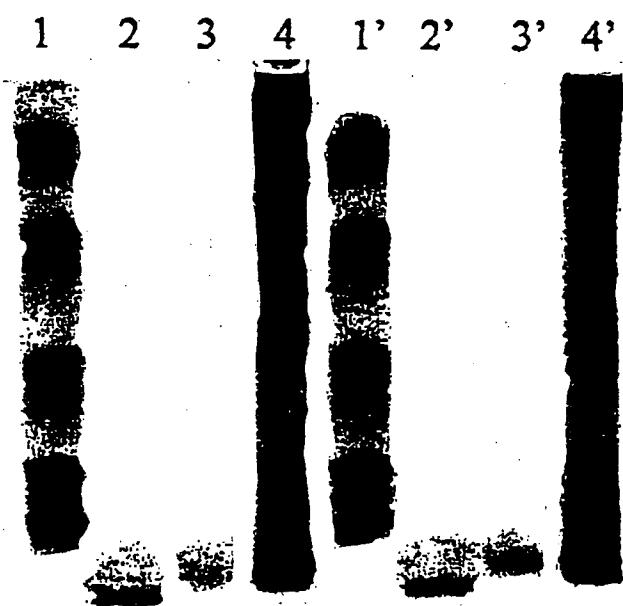


Fig 3

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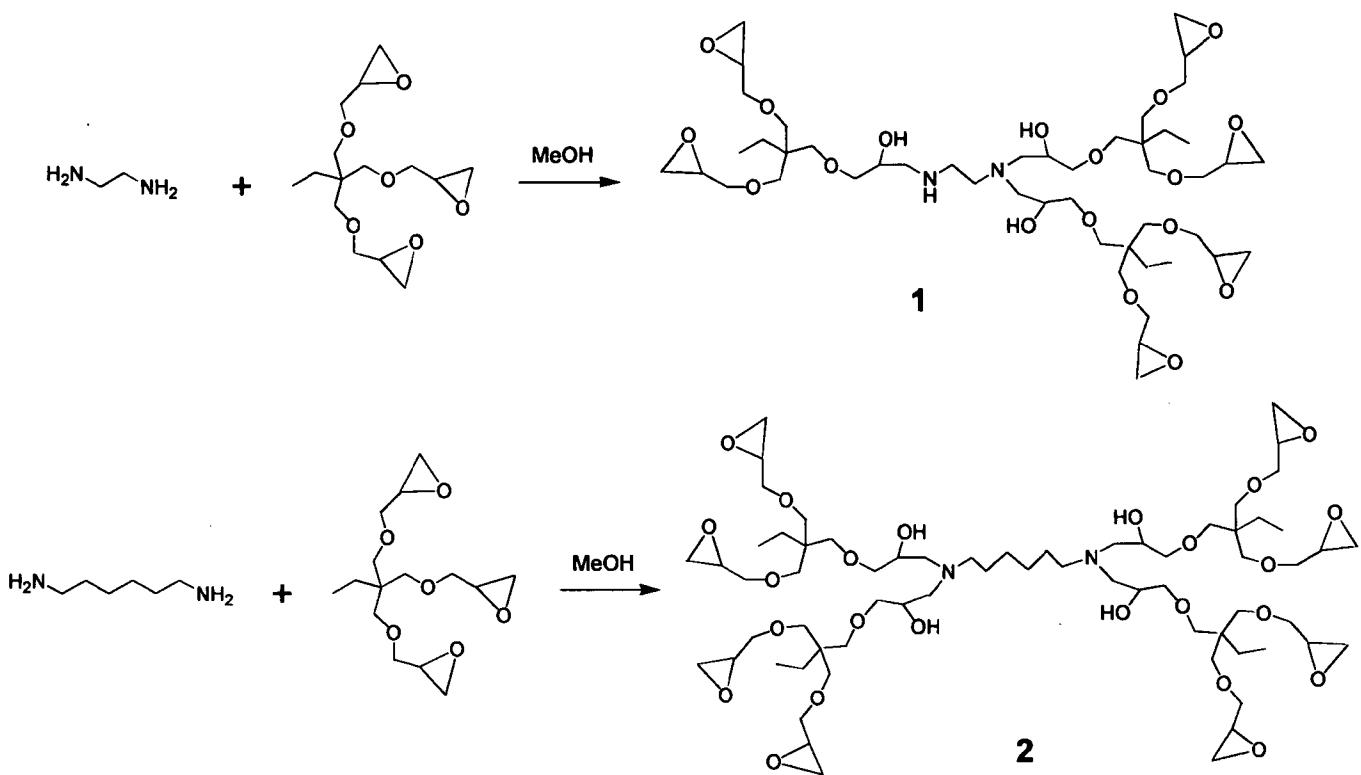


Figure 4

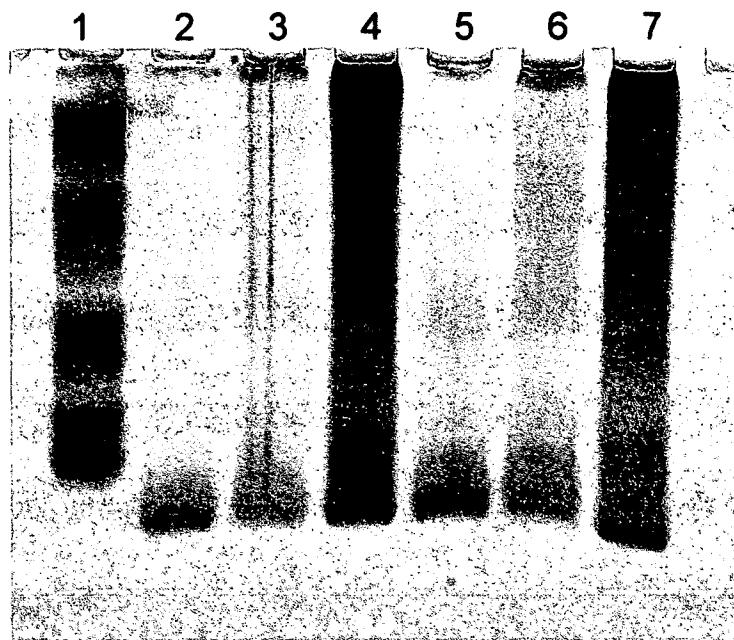


Figure 5

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APPLICATION DATA SHEET

APPLICATION TYPE: Provisional
SUBJECT MATTER: Poly Dendrons/Dendrimers
TITLE: AMINE CORE POLY(ESTER-ACRYLATE)
AND POLY(ESTER-EPOXIDE)
DENDRONS/DENDRIMERS AND THEIR
DERIVATIVES
ATTORNEY DOCKET NUMBER: MSH-294P
SUGGESTED DRAWING FIGURE: Figure 1
TOTAL DRAWING SHEETS: 4
SMALL ENTITY: Y

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